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Image 1617

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Doris HUBLER et al.

Examiner: WEBMAN, Edward J.

Serial No.: 09/719,221

Group Art Unit: 1617

Filed: February 16, 2001

Title: PHARMACEUTICAL COMBINATION USED TO COMPENSATE FOR A TESTOSTERONE DEFICIENCY WHILE PROTECTING THE PROSTATE

REPLY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIR:

In response to the Advisory Action mailed on December 24, 2003, applicants request the continuing examination (RCE) of the application.

As a submission, attached is a reference, e.g., *Brown*, Prostate Cancer, US Pharmacist, 70-82, July 1994, stating on page 75, last paragraph of last column, that "Currently, no data exists to support a causal relationship between benign prostatic hypertrophy (BPH) and prostate cancer." Additionally, attached is the abstract of a reference, e.g., *Auselo et al.*, Cancer of the Prostate. 1. Epidemiology, Prog. Urol., 31-37, February 1995, stating that "neither the presence of benign prostatic hypertrophy, nor the characteristics of the sex life or a history of vasectomy appear to influence the incidence of prostatic cancer."

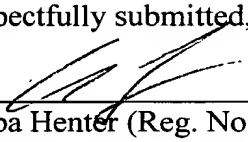
Applicants incorporate their arguments herein from the reply filed November 19, 2003.

The newly submitted material supports the assertion that one of ordinary skill in the art in view of the overwhelming evidence to the contrary of the statements in *Horrobin* would not believe the teaching of *Horrobin* at the time the invention was made on the issue of increased risk for prostate cancer for those affected by BPH.

Applicants submit that none of the prior art references alone or together teach or suggest the claimed invention. Thus, the claims are not obvious.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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Filed: January 20, 2004

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Cancer of the prostate. 1. Epidemiology
MED 03-01 95235576 NDN- 237-0061-2691-7

Mottet Auselo, N.; Costa, P.; Le Pellec, L.; Louis, J. F.; Navratil, H.

JOURNAL NAME- Prog Urol
1995 Feb
PP. 31-7
83 reference(s)
DOCUMENT TYPE- Journal Article; Review; Review, Tutorial
JOURNAL CODE- 9307844
JOURNAL SUBSET- MEDJSIM
ISSN- 1166-7087
CORPORATE AUTHOR- Service d'Urologie Andrologie, CHU G. Doumergue, N.mes.
PUBLICATION COUNTRY- FRANCE
LANGUAGE- French

Prostatic cancer is the second most frequent cancer in men in France. It is a serious disease with a relative 5-year survival of 42%. Although the incidence of latent forms appears to be constant throughout the world, the incidence of clinical forms varies from country to country and according to race. These aspects are in favour of a dual mechanism of prostatic carcinogenesis: initiation of a cellular modification, which may be transmitted genetically according to an autosomal dominant mode, but whose expression may be influenced by the environment, and successive steps of transformation (epigenetic factors) which are essentially environment-dependent. The main identified risk factors essentially consist of a direct family history, age and a diet rich in animal fats. In contrast, neither the presence of benign prostatic hypertrophy , nor the characteristics of the sex life or a history of vasectomy appear to influence the incidence of prostatic cancer. The main epidemiological data currently available are presented.

MEDICAL DESCRIPTOR(S)- Prostatic Neoplasms --EP
SECONDARY MEDICAL DESCRIPTOR(S)- Aged; Aged, 80 and over; Androgens --BL; English Abstract; France --EP; Human; Male; Middle Age; Prostatic Hyperplasia --EP; Prostatic Neoplasms --GE; Risk Factors; Sex Behavior; Vasectomy --SN
CAS SUBSTANCE NAME(S)- Androgens
MESH Z TREE NUMBER(S)- C04.588.945.440.770; C12.294.260.750; C12.294.565.625; C12.740.800.410.650

Prostate Cancer

Sharon Brown, M.S., R.Ph.

Prostate cancer is the most common cancer found in American males. It is second only to lung cancer as the leading cause of cancer deaths in American men. It is estimated that in 1993, 165,000 new cases of prostate cancer were diagnosed.[1] Despite the increasing incidence and high mortality associated with this disease, detection and optimal treatment are controversial issues due to the fact that this particular cancer occurs in latent form in as many as one-third of men over the age of 50. Thus the major considerations are which patients will ultimately develop symptomatic disease and when active treatment should be started to provide the most benefit to the patient.

Risk Factors

Two strong predictors of prostate cancer risk are age and race. Prostate cancer is uncommon in men under 50 years old. The incidence increases with increasing age. The magnitude of the problem is expected to worsen as a result of the aging of the U.S. population. Black American men have the highest incidence rates of prostate cancer in the world, a statistic for which no clear explanation has been determined.[2]

As is the case with many other malignancies, environment

U.S. Pharmacist/University of Wisconsin Continuing Education

Goal: *To help the pharmacist become familiar with etiology and therapy of prostate cancer.*

Objectives: *Upon the completion of this article, the pharmacist should be able to:*

Define *the population of risk for the development of prostate cancer.*

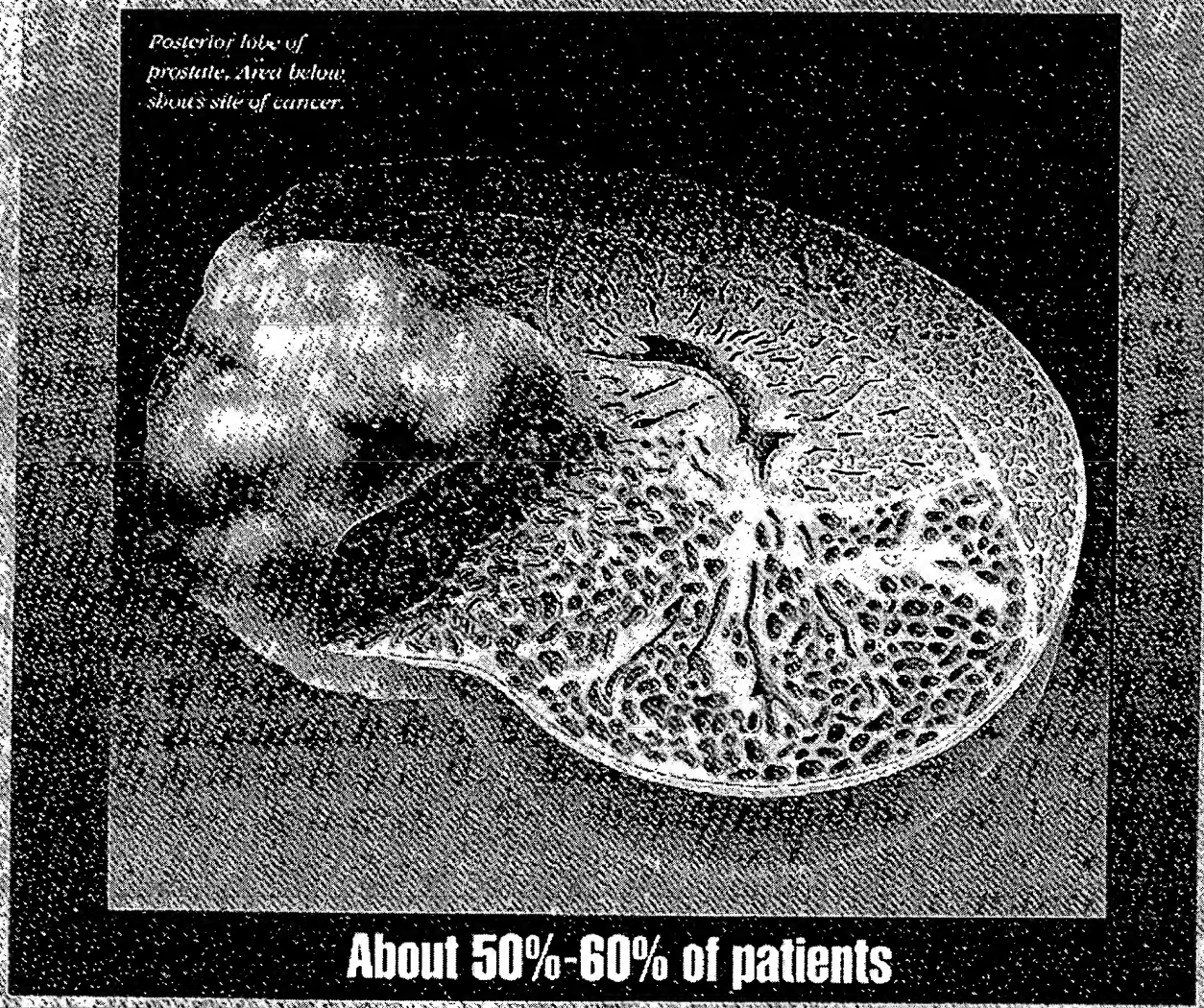
List *three methods of detecting prostate cancer.*

Describe *the relationship between benign prostatic hypertrophy and prostate cancer.*

List *treatment options for the management of localized prostate cancer.*

List *treatment options for the management of metastatic prostate cancer.*

Describe *the role of the pharmacist in public education regarding prostate cancer.*



About 50%-60% of patients

who are diagnosed with the disease

will have advanced cases.

appears to be another factor associated with increased incidence of prostate cancer. This is supported by the fact that males from geographic locations with low clinical prostate cancer incidence have increased rates of prostate cancer after relocation. Since the prevalence of latent disease does not differ significantly by geographic location, it appears that some environmental stimulus converts latent prostate cancer to clinically active disease. This stimulus, however, has yet to be defined.[2]

Other risk factors associated with prostate cancer include high fat diet, family history of prostate cancer, prior sexually transmitted disease and occupational exposure to cadmium.

Pathophysiology

The prostate gland is located between the neck of the bladder and the urogenital diaphragm. Normal growth and differentiation are dependent upon the presence of androgens, especially dihydrotestosterone. The adrenal glands and the testes serve as the primary source of these androgens and are subject to hormonal regulation mediated through biofeedback mechanisms involving the hypothalamus, pituitary, adrenal glands and testes. This biofeedback mechanism involves luteinizing hormone-relesing hormone, luteinizing hormone and follicle stimulating hormone.

Testosterone accounts for approximately 95% of circulating androgens in males and is produced primarily in the testes. However, less than 5% of circulating testosterone is physiologically active. The remainder is bound to a hormone-binding globulin. In addition, the precursors to testosterone androstenedione and dehydroepiandrosterone, are produced in the adrenals. This complicated regulation and production scheme provides the basis upon which hormonal therapies for prostate cancer are based.

Sharon Brown, M.S., R.Ph.
Drug Information Specialist, St. Luke's Hospital, Houston, TX

Detection and Diagnosis

There are three widely accepted diagnostic procedures for prostate cancer determination. They are digital rectal examination, prostate specific antigen and transrectal ultrasonography.

Digital Rectal Examination (DRE): A DRE consists of palpating the posterior lobe of the prostate to evaluate size, configuration and consistency of the gland. This procedure can be done quickly at a relatively low cost. Most prostate cancers develop in this area and can be detected. DRE is not specific for prostate malignancy. However, any palpable abnormalities can be identified for further follow-up. An annual DRE can result in the detection of prostate cancer at an earlier, potentially more curable stage for selected individuals.[3,4]

Prostate Specific Antigen (PSA): PSA is a glycoprotein derived exclusively from prostate epithelial tissue and is considered a very sensitive tumor marker.[5] Elevated PSA levels are not necessarily diagnostic for prostate cancer, since many patients with benign prostatic hypertrophy (BPH) have elevated PSA levels. In addition, some patients with prostate cancer will have normal PSA levels. For this reason, the exact role of PSA determinations in prostate cancer detection has been somewhat controversial. However, recent reports of data collected as a result of Prostate Cancer Awareness Week, a program initiated by the Prostate Cancer Education Council, indicate that PSA has a definite role in early prostate cancer detection. The combination of PSA and DRE resulted in more stage A cancers being detected.[6] Separate studies have compiled data to produce age-specific PSA reference ranges.[6,7]

Transrectal Ultrasonography (TRUS): TRUS uses high-resolution, high-frequency transducers in two different planes to identify prostate abnormalities. The exact role of TRUS in prostate cancer detection remains somewhat controversial. TRUS has the advantages of being able to detect nonpalpable malignancies that are missed by DRE and also can provide data to assist with the staging of cancer detected. However, because of its low positive predictive value, it cannot be recommended as the only screening modality for early detection.[8] The National Prostate Cancer Detection Project is currently attempting to develop standards for prostate cancer detection using TRUS.

BPH and Prostate Cancer

Currently, no data exists to support a causal relationship between benign prostatic hypertrophy (BPH) and prostate cancer. The two conditions are, however, similar in a number of ways. The incidence and prevalence of both increases with age and both are dependent on androgenic hormones for development and growth. Patients undergoing transurethral resection of the

prostate (TURP) for BPH are diagnosed with prostate cancer approximately 10% of the time. However, many of these are low grade or truly latent cancers with potentially minimal impact on the general health of the patient. Most clinicians recommend that patients being managed by non-surgical techniques for BPH should have a DRE and PSA level done as part of a thorough evaluation of prostate cancer status.

Treatment of Prostate Cancer

Localized Disease: The term localized disease, also referred to as clinically organ-confined disease, can be misleading when used to describe prostate cancer. Localized disease may be slow growing and insidious or very aggressive. This category of prostate cancer includes patients who have a good prognosis no matter what course of action the patient takes in regards to therapy, as well as those who are destined to die of their disease because of the aggressive nature of their malignancy.

For patients with localized disease, often the most difficult clinical decision made is whether to treat the patient at all. Patients who have limited longevity as a result of age or other concurrent diseases are not likely to benefit from therapeutic intervention. It has been recommended that a patient life expectancy of at least 10 years be anticipated before definitive therapy is instituted.[9]

The decision to treat localized prostate cancer can be made based upon tumor volume, tumor grade, DNA histograms and other techniques for determining the malignant potential of the tumor. None of these techniques, however, can be uniformly applied for the benefit of this patient population. More often than not, the decision to initiate therapy is based on the individual experience of the clinician involved.

Once a decision to treat has been made, further controversy exists regarding what the most

Table 1

Selected Therapies for Prostate Cancer

TREATMENT CATEGORY	THERAPY	DOSE	SIDE EFFECTS
Surgical intervention	Prostatectomy	N/A	Impotence, incontinence, stricture formation
	Orchiectomy	N/A	
	Adrenalectomy	N/A	
LH-RH or LH Inhibition	DES	1-3 mg/d	Gynecomastia, fluid retention, headache, nausea, vomiting, cardiovascular complications
	Leuprolide	1 mg SQ QD or 7.5 mg IM monthly	Disease flare, hot flashes, sexual dysfunction
	Goserelin	3.6 mg monthly	Disease flare, hot flashes, sexual dysfunction
Androgen Synthesis Inhibition	Aminoglutethimide	250 mg TID-250 mg QID	Lethargy, ataxia, rashes
	Ketoconazole	1200 mg/d	GI upset, transient increases in liver and renal function tests
Antiandrogens	Flutamide	250 mg 8AM	Gynecomastia, GI upset, diarrhea
	Megestrol Acetate	120-160 mg daily	GI upset, weight gain, fluid retention
5-alpha reductase	Finasteride		

Courtesy Kirkwood National Prostate Cancer

appropriate treatment approach is. Radical prostatectomy and external beam irradiation constitute the major treatment options for localized disease.

One comparison of radical prostatectomy and external beam irradiation showed a treatment failure of 10% vs. 40%, respectively.[10] In addition, long term survival rates after radical prostatectomy compare favorably to those obtainable with radiation therapy. For this reason, radical prostatectomy is generally considered the treatment of choice for localized disease in patients who are good surgical candidates.

The major complication of prostate cancer treatment has been post-treatment impotence. However, potency-sparing radical prostatectomy is currently being done with good results, especially in younger patients with localized disease. Another complication most patients fear is incontinence. Current surgical techniques have resulted in postoperative incontinence rates that require intervention in less that 5% of patients.[11]

Metastatic Disease: At the time of diagnosis, 50% - 60% of patients will have advanced disease, with one-third of these patients having metastatic disease.[12] Median survival of patients with distant metastases is two to three years.

The mainstay of therapy for metastatic prostate cancer in the past has been bilateral orchiectomy. This results in the rapid lowering of serum testosterone.[13] It is the treatment of choice for patients with life-threatening complications of the disease such as spinal cord compression or bilateral hydronephrosis, where obstruction of urine flow causes dilation of the pelvis of the kidneys. A bilateral orchiectomy results in diminished pain from bony metastases and a decrease in the size of the prostate in less than two months in most patients. However, patients may not be good candidates for surgery due to advanced age. Other patients find the procedure physically and psychologically unacceptable. If surgical removal of organs responsible for androgen production cannot be accomplished, the hormonal pathways involved in the modulation of prostatic growth can be manipulated with pharmacological agents to induce a state of medical castration similar to prostatectomy. The four mechanisms to accomplish this are the inhibition of luteinizing hormone-releasing hormone (LH-RH) or luteinizing hormone (LH), the inhibition of androgen synthesis, the use of antiandrogens and the use of 5-alpha-reductase inhibitors (TABLE 1).

Since prostate cancer in its early stages is most often clinically non-symptomatic, early detection of the disease is dependent upon the individual taking appropriate measures to screen for this disease. Pharmacists, as the most visible and accessible health care practitioner, can have a significant impact in communities by aiding in efforts to educate and increase public awareness of the disease. Through programs such as Prostate Cancer Awareness Week, held at the end of September each year, pharmacists can offer information and professional advice regarding the benefits of screening and early detection of prostate cancer.

LH-RH or LH Inhibitors: The inhibition of LH-RH or LH results in a reduction in testosterone production. Several pharmacologic agents can be employed to accomplish this. Estrogens directly inhibit the release of LH from the pituitary. Estrogens also exert direct effects on prostate cells and may increase the amount of androgen bound to steroid-binding globulins. Diethylstilbestrol (DES) has been used in the past in doses of 5 mg daily to produce castration levels of testosterone within three weeks of initiating therapy. Early studies showed a reduction in deaths due to prostate cancer when DES was administered at these high doses. Unfortunately, there were increases numbers of deaths due to cardiovascular complications associated with DES.[14] These complications included thromboembolism, congestive heart failure and myocardial infarction. The death rate from these complications offset any survival benefit of estrogen therapy. More recently, studies appear to show that lower doses of 1 mg - 3 mg daily of DES maintains antitumor activity while avoiding the deleterious cardiovascular side effects of the higher dosage regimen.[15]

How early in the disease process estrogen therapy should begin has yet to be determined. The studies described above indicate some benefit to early therapy in younger patients with minimal disease and good performance status.

LH-RH agonists cause a down-regulation of pituitary receptors, resulting in a reduction of serum testosterone levels. These substances are poorly absorbed when administered orally, so al-

ternative routes of administration have been under development. These include subcutaneous and intramuscular injections, long-acting or depot injections and nasal sprays. Currently, depot forms of LH-RH agonists are the preferred route of administration for prostate cancer therapy due to once a month administration, which improves compliance.

Leuprolide was one the first LH-RH agonists tested. Early studies revealed patient responses in up to 40% of previously untreated patients.[16] Currently, a 7.5 mg depot injection is used once a month, with recent response rates up to 86% reported.[17] The incidence of adverse effects is lower than that associated with DES and includes acute flare-ups of bone pain during the first week of therapy and hot flashes.

Goserelin is another LH-RH analogue that is available in a 3.6 mg depot formulation. Response rates as high as 93% have been reported.[18] Once again, increase in bone pain upon initiation of therapy is the major adverse reaction to the drug. Overall reported incidence of side effects was much less than that reported with DES.

Inhibition of Androgen Synthesis: Another mechanism for reducing testosterone levels is to inhibit androgen synthesis in the adrenal gland. Surgical adrenalectomy as associated with a high morbidity and mortality. Therefore, medical adrenalectomy is accomplished with aminoglutethimide or ketoconazole.

Aminoglutethimide inhibits an enzyme in the adrenal gland that is essential for the production of precursors to adrenal-derived steroids. This results in a delay in the progression of disease and symptomatic relief in most patients. Aminoglutethimide in doses used for prostate cancer is most often associated with the side effects of lethargy, ataxia and the development of a morbilliform skin rash. Less commonly reported adverse reactions include hematologic abnormalities (neutropenia, leukopenia, etc.) and metabolic disorders such as changes in lipid profiles and electrolyte imbalances. These are generally reversible with discontinuation of therapy.[19]

Ketoconazole, used primarily as an antifungal agent, inhibits both testicular and adrenal steroid production in a dose-related, reversible manner. In doses of 1200 mg daily, symptomatic relief can be accomplished in previously untreated patients.[20] Ketoconazole has been used effectively in the short term management of prostate cancer, but may not be appropriate for long-term therapy due to the high incidence of side effects associated with the doses required for this indication. These side effects include gastrointestinal upset, transient increases in renal and hepatic function tests, skin rash, myalgias and arthralgias.

Antiandrogens: Antiandrogens work at the cellular level to interfere with androgen-mediated activity. Flutamide is a currently available antiandrogen and several others are under clinical investigation.

Flutamide blocks the binding of testosterone to receptors in the target tissue. Flutamide produces favorable responses in almost 90% of patients, resulting in decreased bone pain, reduction in size of the prostate and improved performance status.[21]

Gynecomastia is the most common side effect related to flutamide therapy. Gastrointestinal upset and diarrhea have also been reported. Flutamide is currently approved for use in the United States in conjunction with an LH-RH agonist such as leuprolide.

Megestrol acetate has been used with some reports of subjective response rates. It has multiple mechanisms of action and in some studies has shown response rates up to 70% when used as initial therapy.[22] However, castration levels of testosterone can be maintained for only short periods of time unless combined with small doses of DES.

5-alpha-reductase inhibitors: 5-alpha reductase works on testosterone to produce dihydrotestosterone (DHT), which binds to androgen-dependent cells. DHT has a higher affinity for these receptors than testosterone. Finasteride, through the inhibition of 5-alpha-reductase, prevents DHT formation, lowering the extent of DHT-receptor complex formation, thus blocking receptor activation. However, while DHT functions are reduced, testosterone-receptor complex activities are not affected. One of the functions DHT facilitates is prostatic growth.[23] For this reason, finasteride is currently approved for the treatment of BPH. It is also in clinical trials for use in advanced prostate cancer. Finasteride is administered in doses of 5 mg daily. The drug is well tolerated. Due to teratogenicity of the drug, precaution should be taken to prevent conception during active treatment with finasteride.[21]

Combination Therapy

Almost all prostate cancer patients relapse within two years of initiation of endocrine therapy.[19] As a result, the concept of total androgen blockade accomplished through combination therapy has been proposed.

Early studies of an LH-RH analogue or orchiectomy to block all sources of testicular steroids, combined with an antiandrogen to block adrenal sources of steroids appeared to be superior to treatment with monohormonal agents,[19,24,25] especially in men with minimal disease. These studies showed some improvement in progression-free survival times and median length of survival for patients treated with a combination of either leuprolide or goserelin plus flutamide, versus leuprolide or goserelin as single agents. Larger trials still need to be conducted to confirm the results of these smaller early trials.

Cytotoxic Chemotherapy

Use of cytotoxic chemotherapy for treatment of prostate cancer is somewhat limited for several reasons. Hormonal therapy is much less toxic and generally better tolerated than cytotoxic chemotherapy. Since most prostate cancer patients are elderly, their ability to tolerate full doses of chemotherapy may be impaired by increases susceptibility to adverse reactions. This results in dosage reductions and less than optimal response to therapy.

Cytotoxic agents that have activity in prostate cancer include cisplatin, cyclophosphamide, doxorubicin, DTIC, 5-fluorouracil and methotrexate.[19] Doxorubicin appears to have the greatest activity, followed by cisplatin. Therapy with single agents produce response rates similar to combination therapy with less toxicity. However, no survival advantage has been demonstrated.

Other Agents

Suramin, a potent transcriptase inhibitor, seems to have antiproliferative effects on cancer cells and has been tried in small groups of prostate cancer patients with variable results.[19]

Liarozole is a new imidazole derivative that interferes with testicular and adrenal testosterone synthesis. Early small studies show an objective response rate of 30% with a well-tolerated side effect profile.[19]

Nilutamide is an antiandrogen that interferes with androgen receptor sites. It is being studied in clinical trials in combination with surgical or medical castration with some early promising results.[26]

Summary: Prostate cancer can be cured when detected in early stages of the disease. Improved detection techniques can help in diagnosis of the disease in early, potentially more treatable stages. Although some controversy exists regarding the optimal therapy for different patient populations, many treatment options are available and good response rates are achievable. Investigations continue to provide objective data about new agents and more optimal utilization of existing therapy to aid clinicians in their choice of treatments.

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EXAMINATION

Select the one correct answer to each of the following questions and record your response on the examination answer sheet. This answer sheet should be removed from the journal and mailed to U.S. Pharmacist, address shown on exam sheet. (Photo copies are acceptable.)

Prostate Cancer

1. Prostate cancer occurs as a latent form of disease:
(A) Most often in men less than 50 years old
(B) In up to 1/3 of men over 50 years old
(C) In all American males
(D) In men with benign prostatic hypertrophy

2. Two of the strongest predictors of prostate cancer risk are:
(A) Geographic location and age
(B) Occupation and race
(C) Age and race
(D) Geographic location and race

3. Approximately 95% of circulating testosterone is physiologically inactive because:
(A) It is bound to hormone-binding globulins
(B) It is stored in the prostate gland
(C) It is bound to prostate-receptors
(D) It is stored in the testes

4. Digital rectal examination:
(A) Is a lengthy procedure when done correctly
(B) Can be done quickly and at a low cost
(C) Must be done every 6 months to be useful
(D) Is specific for prostate malignancy

5. Transrectal ultrasonography:
(A) Is considered the best method for detecting prostate cancer
(B) Has a high positive predictive value
(C) Can aid in staging prostate cancers discovered
(D) Has no advantages over other detection methods

6. Benign prostatic hypertrophy and prostate cancer:
(A) Have no causal relationship
(B) Depend on different mechanisms for growth and development
(C) Should be treated as the same disease
(D) Are always found as co-existent diseases

7. Patients with localized prostate cancer:
(A) Are destined to die of their disease
(B) Have very slow growing tumors
(C) May have rapidly growing or slow growing tumors
(D) Must always be treated to benefit the patient

8. Two major complications of treatment for localized prostate cancer are:
(A) Infection and impotence
(B) Impotence and incontinence
(C) Infection and incontinence
(D) Impotence and disease recurrence

9. The use of bilateral orchiectomy for the treatment of metastatic prostate cancer:
(A) Should be reserved for all patients under the age of 50
(B) Should be reserved for patients of advanced age
(C) Should be reserved for patients who have failed other therapies
(D) Is the treatment of choice for patients with life-threatening complications

10. The use of diethylstilbestrol to treat prostate cancer:
(A) Results in a reduction in testosterone production
(B) Has success only in doses of 5 mg/day
(C) Has shown no benefit in any patient populations
(D) Is most successful when started immediately upon diagnosis

11. Luteinizing hormone-releasing hormone agonists:
(A) Are currently not available to treat prostate cancer
(B) Must be given every day to be effective
(C) Produce more severe side effects than diethylstilbestrol
(D) Are available in convenient once a month dosage forms

12. The inhibition of androgen synthesis:
(A) Can only be accomplished by surgical adrenalectomy
(B) Can be accomplished medically with aminoglutethimide or ketoconazole
(C) Has no benefit in patients with advanced disease
(D) Has no effect on serum testosterone levels

13. 5-alpha-reductase inhibitors:
(A) Are currently approved for the treatment of prostate cancer
(B) Currently have no approved indications in the U.S.
(C) Are currently used to treat benign prostatic hypertrophy
(D) Are not under consideration for use in prostate cancer

14. Using a combination of therapies for prostate cancer management:

(A) Is not currently recommended
(B) May benefit some patient populations
(C) Are thought to be less successful than monohormonal therapy
(D) Only result in increased side effects with no treatment benefit

15. Treatment with cytotoxic chemotherapy:
(A) Is most successful when combination regimens are used
(B) Are less toxic than hormonal therapy
(C) Produce only marginal benefits
(D) Show improved survival over hormonal therapies

16. Prostate specific antigen:
(A) Is considered a very sensitive tumor marker
(B) Is always elevated in patients with prostate cancer
(C) Is always elevated in patients with benign prostatic hypertrophy
(D) Is diagnostic for prostate cancer when levels are elevated

17. The incidence of prostate cancer:
(A) Is expected to drop as a result of improved detection techniques
(B) Has no relationship to environmental factors
(C) Is expected to worsen with the aging U.S. population
(D) Increases with increasing age

18. Patients diagnosed with localized prostate cancer:
(A) Should always consider radical prostatectomy the treatment of choice
(B) Should always consider external beam irradiation the treatment of choice
(C) Should have a life expectancy of 10 years before definitive therapy is started
(D) Will always benefit from some therapeutic intervention

19. Prostate cancer:
(A) Is not considered a curable disease
(B) Is curable when detected in early stages of the disease
(C) Exceeds lung cancer as the leading cause of cancer deaths in American men
(D) Responds to very few treatment modalities

20. Disease flares and hot flashes are associated with the use of:
(A) Androgen synthesis inhibitors
(B) Antiandrogens
(C) 5-alpha-reductase inhibitors
(D) LH-RH inhibitors

U.S. Pharmacist/University of Wisconsin Continuing Education is approved in all states where mandatory continuing education is required. This article has been accredited for two Continuing Education Hours (0.2 CEUs) for each examination successfully completed.

Examination Answer Sheet Enrollment Form

PROSTATE CANCER

Valid for credit until July 1996

Directions: Select one answer to each question in the examination and darken the appropriate circle below using a soft lead pencil.

Detach this answer sheet and mail to:

CONTINUING EDUCATION
U.S. PHARMACIST
P.O. Box 44383
Madison, WI 53744-4383

1.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	11.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
2.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	12.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
3.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	13.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
4.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	14.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
5.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	15.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
6.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	16.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
7.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	17.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
8.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	18.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
9.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	19.	Ⓐ	Ⓑ	Ⓒ	Ⓓ
10.	Ⓐ	Ⓑ	Ⓒ	Ⓓ	20.	Ⓐ	Ⓑ	Ⓒ	Ⓓ

A passing grade of 70% is required. A person who fails an examination may be re-examined at no extra cost.

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If the above is your home address, please provide the name and zip code of the pharmacy where you work:

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( ) This is an address change. My old zip was _____

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PLEASE CHECK ONE: ___$6 per exam fee enclosed
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